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GUIDANCE ON BIOCOMPATIBILITY REQUIREMENTS FOR LONG TERM NEUROLOGICAL IMPLANTS: PART 3 - IMPLANT MODEL

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- **For questions regarding the use or interpretation of this guidance, contact the Orthopedic Devices Branch at 301-594-2036.**
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INTRODUCTION

The requirements specified in this document are of a general nature and may require modification depending on the medical device in terms of its function, intended use and materials of construction. Currently, FDA requires biocompatibility data generated according to Tripartite Biocompatibility Guidance for Medical Devices. Tripartite specifies several toxicity principles to be followed in the selection of materials and toxicity tests to be conducted for the evaluation of medical devices. However, Tripartite is a general document intended for all medical devices and it is often necessary to require additional specialized tests for some devices such as Neurological implants. This guidance document is intended to introduce specialized supplementary tests for long term implanted neurological devices to determine their safety and effectiveness.

Overview

Biological evaluation of medical devices is performed to determine their potential toxicity resulting from contact of device materials with body tissues. The device materials should not, either directly or through the release of their material constituents produce adverse local and systemic effects. Therefore, the evaluation of any device intended for humans requires systematic testing and assessment to give assurance that the final product will perform as intended and is safe for use in humans. Specialized devices, for example, neurological devices, present a unique situation and the general tests (Tripartite) used to evaluate the effects of these devices may not be adequate. The scope of this document is to offer an approach for the evaluation of the biocompatibility of long term neurological implants which have direct contact with brain parenchyma and/or cerebral spinal fluid (CSF).

Neurological devices present an unique challenge for evaluating the biocompatibility of the device materials. Materials safely used in other medical devices not in contact with brain parenchyma or CSF cannot be expected to maintain the same level of biocompatibility without additional supporting data. It is known that CSF and brain parenchyma have increased sensitivity to certain materials which may have reasonable biological performance in other target tissue. For example, brain parenchyma has been shown to exhibit ultra sensitivity to certain metal ions inducing seizure activity in the brain.[2,4]. Therefore, to adequately evaluate the biocompatibility of a long term implant which has direct contact with brain parenchyma and/or CSF specialized testing must go beyond a measured response of the contacting tissue. This testing should include aspects to evaluate physiological and biochemical responses of the Central Nervous System to the presence of implanted devices. For example, specialized testing may be necessary to evaluate the possible sensitivity of the choroid plexus or arachnoid villi to impurities or toxins transported by the cerebral spinal fluid which may impact the natural absorption and secretion of CSF.

STUDY DESIGN

The study should be designed to measure the biological performance of a long term implant and provide supporting data as to the device's biocompatibility with respect to its intended use. A long term implant with direct contact with brain parenchyma and CSF would require the observation of tissue reaction in an animal model to the medical device at the implanted site over a period of time simulating its intended use. In addition, it may be important to include in the model monitoring and observation to evaluate any seizure activity over specified intervals, and evaluate effects on the natural mechanism of absorption and secretion of CSF.

Materials and Methods

Animal Model

The type of animal model chosen for an implant study must be appropriate with respect to its relevance to human physiology and biological response. For example, a canine model may be suitable to measure the effects of a device or material on increased seizure activity in the brain but the same model would not be appropriate to use as an infection model. It is important to recognize species differences in target organ susceptibility or selectivity. Species selectivity in any target organ toxicity study is dependent on many factors including absorption, distribution and metabolism. In addition, factors such as anatomic site should be considered.[3] Therefore, the animal for the study should be appropriate for the intended use of the device.

Number of Animals

The total number of animals used in the study must be specified as well as the number of implants per animal. A sufficient number of animals must be used to establish adequate repeatability and statistical validity of the results. In some circumstances multiple implants may be considered per animal to increase statistical validity. If multiple implants are to be used then it is important to identify each implant site and its orientation to the control.

Study Duration

The total duration of the study should be over a period of time representative of a permanent implant. At a minimum the study must be long enough to document the initial reaction and repair or healing process around the implant site with periodic intervals for sacrifice and examination. However, the anticipated effects of the device and all other influencing factors of the device described above must be considered when justifying the duration of the study.

Methods of Measurement

There are three levels of change in tissue which provide three different approaches to the assessment of toxicity in the system; biochemical, morphological, and physiological[3]. The same fundamental principles of toxicity to any organ applies to neurotoxicity however, there are distinctions of biochemistry, geometry, and function of nervous tissue[3]. As stated previously the nervous system is uniquely susceptible to certain toxic agents requiring specialized techniques for the measurement and assessment of toxicity.

The specific techniques for measurement and assessment of the device's biological performance will depend on the need to measure each level of change in the contact tissue. Whether the method of measurement involves gross and histopathological changes or recordings of EEG or behavioral observation each methodology must be completely described down to the sample preparation, monitoring procedures, explant procedures, assessment criteria, Histo-Pathological procedures, defining intervals of sacrifice, etc.

Controls

The use of positive and negative controls cannot be overemphasized. The use of a control will enhance the built-in sensitivity in the test to detect potential adverse effects. Positive and negative controls should be included and should be tested concurrently with the test sample whenever possible. Positive and negative controls do not have to be included in every repetitive test when the test is performed very frequently and a high level of repeatability can be demonstrated. Specify and describe in detail the control to be used in the protocol.

Results and Statistical Analysis

Interpretation of results must go beyond clinical observation and show a repeatable outcome. Depending on what method of measurement is chosen a statistical analysis demonstrating a statically significant result would be necessary.

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